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Short title: Long-term safety of open-label epratuzumab

Long-term safety and efficacy of epratuzumab in the treatment of moderate-to-severe systemic lupus erythematosus: results from an open-label extension study

D. J. Wallace,[1] K. Hobbs,[2] M. E. B. Clowse,[3] M. Petri,[4] V. Strand,[5] M. Pike,[6] J. T. Merrill,[7] P. Leszczynski,[8] C. M. Neuwelt,[9] S. Jeka,[10] F. Houssiau,[11] M. Keiserman,[12] J. Ordi-Ros,[13] S. Bongardt,[14] B. Kilgallen,[15] C. Galateanu,[16] K. Kalunian,[17] R. Furie,[18] C. Gordon[19, 20]

[1]Division of Rheumatology, Cedars-Sinai Medical Center, Los Angeles, USA; [2]Denver Arthritis Clinic, Denver, USA; [3]Duke University Medical Center, Durham, USA; [4]Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, USA; [5]Biopharmaceutical Consultant, Portola Valley, USA; [6]MedPharm Consulting, Inc., Cambridge, USA; [7]Oklahoma Medical Research Foundation, University of Oklahoma Health Sciences Center, Oklahoma City, USA; [8]Department of Rheumatology and Rehabilitation, Poznan University of Medical Sciences, Poznan, Poland; [9]Division of Rheumatology, Alameda

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County Health System, Oakland, USA; [10]Clinic of Rheumatology and Connective Tissue Diseases, 2nd University Hospital, CM UMK, Bydgoszcz, Poland; [11]Clinique Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [12]Pontifical Catholic University, School of Medicine, Porto Alegre, Brazil; [13]Department of Systemic Autoimmune Diseases, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [14]UCB Pharma, Monheim, Germany; [15]UCB Pharma, Raleigh, USA; [16]UCB Pharma, Brussels, Belgium; [17]UCSD School of Medicine, La Jolla, USA; [18]Division of Rheumatology, North Shore-Long Island Jewish Health System, New York, USA; [19]Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK; [20]NIHR/Wellcome Trust Clinical Research Facility, University Hospital Birmingham NHS Foundation Trust, Birmingham, UK

Correspondence to:

Professor D. J. Wallace

Division of Rheumatology

Cedars-Sinai Medical Center

8737 Beverly Blvd Suite 302

West Hollywood

CA 90048

danielwallac@gmail.com

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ABSTRACT

Objective: The primary objective was to assess the long-term safety of repeated courses of epratuzumab therapy in patients with moderate-to-severe systemic lupus erythematosus. Secondary objectives were to assess long-term efficacy and health-related quality of life (HRQoL).

Methods: Eligible patients from the 12-week, phase IIb, randomized, placebo-controlled EMBLEM™ study (NCT00624351) enrolled into the open-label extension (OLE) study, SL0008 (NCT00660881). In SL0008, patients received 1200 mg epratuzumab infusions at Weeks 0 and 2 of repeating 12-week cycles, plus standard of care. Safety measures included treatment-emergent adverse events (TEAEs) and serious TEAEs. Efficacy measures included combined treatment response, BILAG score, SLEDAI score, physician's and patient's global assessment of disease activity. Total daily corticosteroid dose and HRQoL (SF-36) were also assessed.

Results: 113 of the 203 patients who entered SL0008 (55.7%) continued epratuzumab therapy until study closure (total cumulative exposure: 381.3 patient-years; median exposure: 845 days;

maximum exposure: 1185 days/approximately 3.2 years). TEAEs were reported in 192 patients (94.6%), most commonly infections and infestations (68.0%; 138 patients). Serious TEAEs were reported in 51 patients (25.1%); 14 (6.9%) serious infections. In patients treated for 108 weeks (n=116), median corticosteroid dose was reduced from 10.0 mg/day at OLE screening to 5.0 mg/day at Week 108. Improvements in efficacy and HRQoL measures in EMBLEM™ were maintained in the OLE, while placebo patients exhibited similar improvements in disease activity upon switch to epratuzumab.

Conclusion: Open-label epratuzumab treatment was well-tolerated for up to 3.2 years, and associated with sustained improvements in disease activity and HRQoL, while steroids were reduced.

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SIGNIFICANCE & INNOVATIONS

- Epratuzumab is the first CD22-targeting monoclonal antibody in development for the treatment of moderate-to-severe SLE.
- The results from this open-label extension study show that epratuzumab treatment in addition to standard of care was well-tolerated for up to 3.2 years with no new safety concerns identified.
- Patients who had received epratuzumab therapy in the prior double-blind study maintained their initial improvements in disease activity, and placebo patients exhibited similar improvements in disease activity following switch to epratuzumab.
- In patients receiving epratuzumab therapy for 108 weeks, median corticosteroid dose was halved from baseline.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can cause widespread tissue damage, particularly affecting musculoskeletal, mucocutaneous and renal systems.[1, 2] Since disease progression varies considerably between patients, SLE can be a challenging condition to manage.

The goal of treatment for active moderate-to-severe SLE is to control inflammation and prevent organ damage. Corticosteroids are almost universally effective and are a cornerstone of treatment, however serious long-term complications are associated with their use.[3, 4] Over the last 50 years, understanding of SLE pathogenesis has greatly increased and facilitated the development of therapies that target key immune cells and mediators in SLE. B cells have been recognized to play a critical role in SLE and are therefore an attractive target for new therapeutic agents.[5, 6] Currently only one such agent, belimumab, is licensed for use in moderate-to-severe SLE in the USA and Europe, which inhibits the biological activity of soluble B lymphocyte stimulator (BLyS).[7, 8]

Epratuzumab is a novel B cell modulator. It is a monoclonal antibody that binds CD22, a co-receptor of the B cell receptor (BCR).[9] The biology of CD22 is complex, but there is evidence

that epratuzumab binding induces colocalization of CD22 with the BCR, independent of BCR engagement. This promotes the inhibitory function of CD22 on BCR-mediated signaling and thereby modulates B cell activity with inhibition of B cell activation, but without total B cell depletion.[9-14] The loss of BCR proteins from the B cell surface by mechanisms such as internalization and trogocytosis may further disrupt BCR activation.[10, 13] Recent studies have suggested that the antibody may regulate the balance between regulatory IL-10 and pro-inflammatory cytokines in favor of the former through enhanced IL-10 expression and inhibition of pro-inflammatory IL-6 and TNF-α cytokine production.[15, 16] B cell hyperactivity and altered cytokine production play a pivotal role in active SLE,[17] ergo there is a strong rationale for targeting CD22-mediated B cell signaling in SLE.

The safety and efficacy of epratuzumab have been assessed in the ALLEVIATE-1 and -2 randomized controlled trials (RCTs; NCT00111306 and NCT00383214, respectively), and in the phase IIb EMBLEM™ study (NCT00624351). Although the ALLEVIATE trials were terminated early due to interruptions in medication supply, at Week 12 a higher proportion of patients receiving 360

mg/m^2 epratuzumab achieved a British Isles Lupus Assessment Group (BILAG) response compared to patients receiving either placebo or 720 mg/m^2 epratuzumab.[18] No aberrant safety signals were identified.[18] Epratuzumab-treated patients also reported greater improvements in HRQoL than those receiving placebo.[19]

In EMBLEM™, a 12-week dose-ranging RCT, epratuzumab treatment was associated with clinically meaningful improvements in disease activity in moderate-to-severe SLE patients, with no new safety signals observed (EMBLEM™ was not powered to detect statistically significant improvements between treatment arms).[14] Eligible patients entered the EMBLEM™ open-label extension (OLE) study, SL0008 (NCT00660881), and continued receiving epratuzumab therapy. Here, we report the results from this OLE study on the safety and clinical outcomes observed in patients receiving epratuzumab for up to 3.2 years.

METHODS

Study design

Entry criteria and design of the EMBLEM™ study have been published previously.[14] Briefly, the phase IIb double-blind, placebo-controlled, 12-week study enrolled adult (≥18 years) patients with

active SLE who were positive for anti-nuclear antibody at screening and had received corticosteroids at a stable dose of 5-60 mg/day (prednisone equivalent) for ≥5 days before the first dose of study medication. Enrolled patients had moderate-to-severe SLE, demonstrated by a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K)[20] score of ≥6, and either BILAG-2004 index[21] A grade (severe) disease activity in ≥1 body system (except renal or central nervous system), or BILAG B grade (moderate) disease activity in ≥2 body systems. At least one of the BILAG A grades, or ≥2 of the BILAG B grades must have been in the mucocutaneous, musculoskeletal or cardiorespiratory BILAG-2004 index domains.

In EMBLEM™, patients were randomized to receive placebo or one of 5 epratuzumab dosing regimens (100 mg every other week [Q2W], 400 mg Q2W, 1200 mg Q2W, 1800 mg Q2W or 600 mg weekly [QW]) plus standard of care, with infusions delivered over the first 4 weeks of the 12-week study (Figure 1). Patients who completed the RCT or who discontinued blinded treatment due to lack of efficacy but completed ≥8 weeks of the RCT, were eligible to enter the OLE study, SL0008. SL0008

consisted of repeating 12-week treatment cycles (1200 mg infusion at Weeks 0 and 2; Figure 1) plus standard of care. The study was terminated early to consolidate the ongoing open-label extension studies from the EMBLEM™ and ALLEVIATE trials: patients had the option to enroll into another ongoing phase III long-term extension study, SL0012 (NCT01408576). Here we report results from the EMBLEM™ OLE study.

The SL0008 study protocol was reviewed by an independent ethics committee or institutional review board for each site and was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice requirements and local laws. All patients gave their informed written consent before taking part.

Safety assessments and analyses

The primary objective of SL0008 was to assess the safety of repeated courses of epratuzumab therapy (1200 mg at Weeks 0 and 2) given in 12-week treatment cycles (maximum exposure of 1185 days/approximately 3.2 years; median exposure 845 days/approximately 2.3 years). Analyses were performed on the

safety population, defined as all patients who had received at least 1 dose (or partial dose) of epratuzumab. Safety measures included treatment-emergent adverse events (TEAEs) and serious TEAEs classified by system organ class (SOC) and preferred term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA) v.15.0. TEAEs occurring in ≥5% of patients by PT, and serious TEAEs occurring in ≥1.5% of patients by SOC and PT, as well as exposure-adjusted incidences, are reported. Discontinuations due to TEAEs are presented by MedDRA SOC and PT.

A TEAE was classified as serious if it resulted in death, was life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant disability/incapacity or was a congenital anomaly or birth defect. Additionally, any important medical event that may not have been life-threatening or resulted in death or hospitalization could be classified as serious if, based on appropriate medical judgment, it may have jeopardized the patient or required medical or surgical intervention to prevent one of the other outcomes. Pregnancies were dated and reported from the last menstrual period.

Efficacy and HRQoL evaluations

The secondary objectives of SL0008 were to assess efficacy and changes in SLE disease activity and HRQoL assessed by Medical Outcomes Short-Form (SF-36) survey with prolonged epratuzumab treatment. Efficacy variables assessed included BILAG improvement without worsening, combined treatment response, BILAG score (BILAG-2004 Index),[21] SLEDAI-2K score[20] and physician's and patient's global assessment of disease activity (PGA and PtGA; 100 mm visual analogue scale).

Treatment response in this study was based on a modified version of the BILAG-based Composite Lupus Assessment (BICLA) composite endpoint,[22] and was defined as BILAG improvement without worsening, and no worsening in SLEDAI-2K or PGA. The fourth criterion of BICLA, "no treatment failure," was not included. BILAG improvement without worsening was defined as all A scores at baseline improved to B/C/D, and all B scores improved to C/D, with no worsening in other BILAG organ systems such that there were no new A scores and ≤1 new B score. No worsening in PGA was defined as less than 10% worsening. Efficacy variables were captured at EMBLEM™ baseline and OLE

screening, at 4-week intervals through Week 48, then at 12-week intervals and at the last study visit. Total daily corticosteroid dose was summarized at 4-week intervals throughout and converted to prednisone equivalent prior to analysis.

HRQoL was measured using the SF-36. Assessments were carried out at EMBLEM™ baseline and SL0008 screening in all randomized EMBLEM™ patients, and at 12-week intervals during the study and at the last study visit in the SL0008 safety population. Minimum clinically important differences were defined as ≥2.5-point increases from EMBLEM™ baseline for physical component summary (PCS) and mental component summary (MCS) scores and ≥5.0 points in domain scores where increases in scores signal improvement.[23-26]

Statistical analysis

The safety population was analyzed using SAS® (SAS Institute, Version 9.1.3 Service Pack 4, Cary, NC, USA). Summary statistics are presented. No inferential analyses were conducted. Sample size was not determined on the basis of formal statistical calculations, as the primary objective of this study was to continue to evaluate safety in eligible patients from EMBLEM™.

Missing components of combined treatment response were imputed using last observation carried forward for a maximum of one visit, and thereafter treated as missing. Missing values of SF-36 domain scores were imputed using last observation carried forward from EMBLEM™ baseline to SL0008 screening. All other observed data are reported with no imputation of missing data.

Comparisons to both EMBLEM™ baseline and SL0008 screening are reported for efficacy and HRQoL evaluations. Changes from baseline are reported as changes from EMBLEM™ baseline in those patients included in SL0008. Data are presented to Week 108: the last time-point at which >50% of patients reported data for combined treatment response, and are also presented for the last visit, giving the last available value for each patient regardless of when the last visit occurred.

RESULTS

Patient disposition and baseline characteristics

Of the 203 patients who entered SL0008, 113 (55.7%) continued epratuzumab infusion until study closure (Figure 1) and 90 patients (44.3%) withdrew from the study. The most common reasons for withdrawal were TEAEs (29 patients; 14.3%; of which

7 were pregnancies), withdrawal of consent (25 patients; 12.3%), lack of efficacy (23 patients; 11.3%) and loss of efficacy (5 patients; 2.5%). Withdrawals over time are shown in Supplementary Figure 1. One death occurred during the study, which was deemed unlikely to be related to the study drug (discussed below).

Patient characteristics and demographics at the start of SL0008 are summarized in Table 1. Patients receiving concomitant medications for SLE included corticosteroids (191 patients; 94.1%), immunosuppressives (90 patients; 44.3%) and antimalarials (88 patients; 43.3%) (Table 1).

Exposure to epratuzumab

Total cumulative exposure to epratuzumab across both EMBLEM™ and SL0008 was 381.3 patient-years; median duration of epratuzumab exposure in SL0008 was 845 days (range: 75-1185 days), approximately 2.3 years median and 3.2 years maximum exposure.

Summary of adverse events

During SL0008, TEAEs were reported in 192 patients (94.6%), the majority of which were mild or moderate in intensity; 51 patients (25.1%) had severe TEAEs (Table 2). Over the study period, TEAEs in 87 patients (42.9%) were assessed as related to the drug (Table 2) and 29 patients (14.3%) withdrew due to TEAEs; commonest causes were lupus nephritis (6 patients; 3.0%) and SLE flare (5 patients; 2.5%).

Summaries of all TEAEs with an incidence of at least 5% in the safety population by MedDRA SOC and PT are provided in Table 3. The most common TEAEs reported by SOC were infections and infestations (68.0%), and the most common TEAEs by PT included urinary tract infection (24.6%), upper respiratory tract infection (23.2%), headache (19.7%), sinusitis (10.8%), and nausea and asthenia (9.9% each; Table 3).

Serious TEAEs with an incidence of at least 1.5% in the safety population by MedDRA SOC and PT are provided in Table 4. A total of 98 serious TEAEs were reported in 57 patients (28.1%). The most commonly reported serious TEAE by SOC were

infections and infestations (14 patients; 6.9%) discussed further below. The most common serious TEAEs reported by PT were SLE flares (7 patients; 3.4%), followed by lupus nephritis (4 patients; 2.0%) and symptomatic cholelithiasis (3 patients; 1.5%). One death, which was considered unrelated to the study drug by the investigator, occurred during the study; a postmenopausal 43-year-old Caucasian female with a past medical history of osteoporosis and hypertension experienced a serious TEAE with echocardiographic signs of pericarditis 43 days after the most recent infusion of epratuzumab and 57 days after the first infusion. Although the patient first recovered, her condition worsened dramatically shortly after discharge and she subsequently died. The cause of death was considered high-grade chronic heart failure.

Adverse events considered of particular interest

Infections

The most commonly reported infections were urinary tract infection (50 patients, 24.6%), upper respiratory tract infection (47 patients; 23.2%) and sinusitis (22 patients; 10.8%) (Table 3). Although 14

patients reported serious infections, most were single cases in individual patients; the only serious infections reported in more than one patient were gastroenteritis, sepsis and urosepsis (2 patients each; 1% each). There were no reported events of pneumonia, Herpes zoster or tuberculosis and only one reported event of *Clostridium difficile* colitis.

Neoplasms

Neoplasms (benign, malignant or unspecified) were reported in 3 patients during the study. These included thyroid neoplasm in 2 patients (small nodules on the thyroid in one, and tiny bilateral hypoechoic thyroid nodules in the other) and basal cell carcinoma, breast cancer, and malignant lip neoplasm (stage unspecified) in a single patient.

Lupus nephritis

Lupus nephritis developed in 7 patients (3.4%), 4 of which were classified as serious TEAEs (one was confirmed by biopsy). Six of the patients discontinued the study; but one patient continued the study, despite nephritis being classified as serious. Only one

patient had a prior history of renal disease, with previously confirmed membranous lupus glomerulonephritis class V.

Pregnancies

Seven women (3.4%) became pregnant over the course of the study, discontinued epratuzumab and withdrew from the study. Of these patients, 2 delivered healthy full-term babies, 2 underwent induced terminations, one miscarried (suspected ectopic pregnancy 8 weeks after receiving the last dose of epratuzumab, which miscarried at 47 days gestation) and 2 delivered premature babies at 32 weeks gestation. One of these patients became pregnant 2 days after receiving the last dose of epratuzumab, was hospitalized due to SLE at 30 weeks gestation, and underwent a cesarean section due to preeclampsia. The baby died 2 weeks after delivery due to an unconfirmed pulmonary hemorrhage. The other became pregnant 13 days after receiving the last dose of epratuzumab, had an early cesarean section despite no reported pregnancy complication and delivered a healthy baby.

Corticosteroid use

Median corticosteroid dose was 10.0 mg/day (range: 0.0–60.0 mg/day) at both EMBLEM™ baseline and SL0008 screening, which was decreased to 5.0 mg/day (range: 0.0–40.0 mg/day) in the patients remaining in the study at Week 108 of the OLE (Figure 2A). The proportion of patients requiring corticosteroid doses of >17.5 mg/day decreased from 28.6% at EMBLEM™ baseline and 21.2% at SL0008 screening to 12.1% at Week 108 (Supplementary Figure 2). Conversely, the proportion of patients receiving >0.0–5.0 mg/day increased from 27.6% at EMBLEM™ baseline and 26.1% at SL0008 screening to 39.7% at Week 108, and the proportion of patients not receiving any corticosteroids also increased from 2.0% at EMBLEM™ baseline and 5.9% at SL0008 screening to 12.1% at Week 108 (Supplementary Figure 2).

These are observed data, so may be affected by patient discontinuation. Thus the corticosteroid dose at the last visit for each patient was analyzed regardless of the time that this occurred. At the last visit, the median corticosteroid dose was 10.0 mg/day (Figure 2A), the same as at SL0008 entry. However,

the proportion of patients requiring a dose ≤7.5 mg/day increased, and the proportion taking >7.5 mg/day decreased compared to EMBLEM™ baseline (Supplementary Figure 2).

To assess corticosteroid-sparing effects in those who remained in the study to Week 108 (n=116), a separate analysis was performed. Median corticosteroid dose at EMBLEM™ baseline and at SL0008 screening in these patients was 10.0 mg/day (range: 0.0–50.0 mg/day). At Week 48 of the OLE, median corticosteroid dose had decreased to 5.5 mg/day (range: 0.0–40.0 mg/day) in these patients and remained stable to 5.0 mg (range: 0.0–40.0 mg/day) at Week 108.

Efficacy endpoints

During SL0008, the observed percentage of patients with BILAG improvement without worsening, compared to EMBLEM™ baseline, increased over time from 34.5% at SL0008 screening to 63.8% at Week 108. At their last visit, regardless of when this occurred, BILAG improvement without worsening was seen in 48.3% of patients.

The percentage of patients achieving a combined treatment response (defined as BILAG improvement without worsening, and no worsening in SLEDAI or PGA) increased during SL0008. This was most pronounced in EMBLEM™ placebo patients (Figure 2B) who exhibited responses comparable to those who received active treatment in the EMBLEM™ trial. Response rates increased from 25.7% at SL0008 screening to 45.7% at the last visit in those patients who had originally received placebo during EMBLEM™, and from 33.9% at SL0008 screening to 40.7% in those who received epratuzumab in EMBLEM™.

Median total BILAG score of the treated population decreased from EMBLEM™ baseline and remained stable throughout SL0008 (Figure 2C). At the last visit, the median total BILAG score was 10.0 (range: 0–72), compared to 14.0 (range: 0–57) at SL0008 screening. In patients who remained in the study at Week 108, the median total BILAG score was 9.0; a decrease of 64% from the median total BILAG score of all patients at EMBLEM™ baseline.

The proportion of patients who improved from maximum BILAG system grades A or B at EMBLEM™ baseline to BILAG grades C

or D at Week 108 of SL0008 exceeded 60% in the musculoskeletal, mucocutaneous, cardiorespiratory, constitutional and renal domains (observed data, Supplementary Figure 3).

Median SLEDAI score also decreased from EMBLEM™ baseline to Week 108 of SL0008 (Figure 2D). At the last visit for each patient, the median total SLEDAI score was lower than that at SL0008 screening (last visit: 8.0 [range: 0–32]; OLE screening: 10.0 [range: 0–34]). At Week 108, approximately two thirds of patients remaining in the study had at least a 4- or 6-point improvement in SLEDAI compared to EMBLEM™ baseline (Supplementary Table 1). Improvements in SLEDAI of at least 8 points were seen in 46.8% of patients at Week 108 and, at the last visit, in 39.7% of patients (Supplementary Table 1).

Both PGA and PtGA improved (Supplementary Table 1). A decrease from EMBLEM™ baseline was observed in median PGA score until Week 48 of SL0008, and remained stable through Week 108. Median PGA score at the last visit was 25.0 (range: 0–94), 50% less than EMBLEM™ baseline (50.0, range: 0–90). Similarly, median PtGA scores improved from 53.0 (range: 1–90) at EMBLEM™ baseline to 41.0 (range: 0–95) at SL0008 screening,

and continued to improve during SL0008 to 34.0 (range: 1–81) at Week 108. At the last visit for each patient, median PtGA score was similar to that at SL0008 entry (40.0, range: 1–97). Physician assessment seemed to correspond with the patients' assessment of their disease; median changes from baseline in PGA and PtGA at the last visit were -23.0 (range: -65–57) and -9.0 (range: -75–96), respectively.

HRQoL

Mean SF-36 PCS and MCS scores increased from SL0008 screening to Week 48, and were maintained to Week 108 (Supplementary Figure 4A). Change from EMBLEM™ baseline in PCS and MCS were clinically meaningful (≥2.5 points) at all time points measured up to Week 108. At Week 108, the percentage of those with a clinically meaningful improvement from EMBLEM™ baseline in PCS and MSC was 70.8% and 59.3% of patients, respectively. At the last visit for each patient, 61.9% achieved clinically meaningful changes in PCS, and 44.1% achieved clinically meaningful changes in MCS.

Increases from EMBLEM™ baseline in all SF-36 domain scores were observed at SL0008 screening in all patient groups, including those who received placebo in EMBLEM™. SF-36 domain scores were further increased with clinically meaningful changes from baseline to Week 48, and maintained or further improved up to Week 108, indicating improved HRQoL (Supplementary Figure 4B).

DISCUSSION

In this open-label extension study, SLE patients received epratuzumab for a median of 2.3 years (maximum 3.2 years), giving a total exposure of more than 380 patient-years. No new safety signals were identified, and the one death that was reported (due to chronic heart failure) was deemed by the investigator as unlikely to be related to the study drug. Serious infections and infestations were reported in 14 patients (6.9%), with no incidences of pneumonia, Herpes zoster or any cases of tuberculosis.

The improvements in disease activity seen in EMBLEM™ were maintained through the OLE. This was seen in multiple individual

BILAG organ systems, and by SLEDAI (assessed by reduction in median score and increasing proportion of patients with significant reductions of SLEDAI score), as well as PGA, demonstrating breadth of response. Patients who had received placebo in EMBLEM™ also exhibited rapid improvements in disease activity following a switch to epratuzumab treatment at SL0008 entry, as measured by combined treatment response, consistent with the response in epratuzumab-treated patients in EMBLEM™.[14] Most patients who continued receiving epratuzumab therapy throughout the study were able to reduce their dose of concomitant corticosteroids, while maintaining reductions in BILAG score.

During SL0008, 5 patients (2.5%) withdrew due to loss of efficacy, and 23 (11.3%) due to lack of efficacy. Those whose withdrawal was attributed to TEAEs of lupus flare (2.5%) or nephritis (3.0%) should also be considered non-responsive to the treatment. The remainder withdrew due to other TEAEs, withdrawal of consent, protocol violation or other reasons.

In the 55.7% of patients who remained on treatment in the OLE, clinically meaningful improvements in PtGA and HRQoL observed in EMBLEM™[27] were sustained long-term (up to 3.2 years).

Although discordance in physician and patient global assessments of disease activity has been previously observed in SLE (a difference of ≥25 mm on a 0–100 mm scale is considered clinically meaningful),[28] here there was concordance between patients' and physicians' assessments of disease activity, indicated by median PtGA and PGA scores, and similarly shown by HRQoL and the specific lupus disease activity indices.

This study was not without limitation: sources of bias, imputation methods, comparison group, validated questionnaires and the size of the study population are discussed. The potential bias introduced by patient dropout is inherent in the open-label design of this study, since discontinuation due to lack of efficacy could positively skew observed results. Patient retention in this study was 55.7% at the time of study closure. Inclusion of data from the last visit, giving the last available value for each patient regardless of when the last visit occurred, can give some perspective on the impact of dropout bias. Here, conservative imputation methods were used; the only missing data imputed were individual components of combined treatment response, which were carried forward a maximum of one visit, and missing values

of SF-36 domain scores, which were carried forward from EMBLEM™ baseline to SL0008 screening only. Additionally, in a study in which all patients receive study drug, no comparisons are available with patients treated with community standard of care without epratuzumab. Validated patient-reported outcomes (PROs) specific to lupus such as LupusPRO, Lupus Impact Tracker (LIT) and LupusQoL were not available when the study was initiated,[29-31] and may have provided further insight into HRQoL. The results of phase III trials, utilizing larger patient cohorts, will provide further important safety information, given that there were relatively small numbers in this OLE study.

Open-label epratuzumab treatment was found to be well-tolerated with extended use up to 3.2 years, giving a total patient exposure of over 380 patient-years. At the time of study closure, 55.7% of patients were still receiving epratuzumab therapy. In those receiving epratuzumab for 108 weeks, the median corticosteroid dose was reduced from 10.0 mg/day at EMBLEM™ baseline and SL0008 screening to 5.0 mg/day. Improvements in efficacy and HRQoL seen in EMBLEM™ were maintained over the duration of the SL0008 study. These results strongly support the

continued study of epratuzumab for the treatment of patients with moderate-to-severe SLE.

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CONTRIBUTIONS

DJW was the principal/coordinating investigator. BK was the study statistician. SB was the Clinical Program Director. DJW, MEBC, CGo, KH, FH, SJ, MK, PL, CMN and JO recruited patients and acquired data. DJW, SB, MEBC, RF, CGo, KH, KK, BK, PL, JM, CMN, MPe, MPi, VS and CGa analyzed and interpreted the study data. All authors critically reviewed the manuscript, approved the final version for submission and agree to be accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

AUTHOR DISCLOSURES

DJW: Consultant for Biogen, GlaxoSmithKline and UCB Pharma

KH: Consultant for UCB Pharma

MEBC: Consultant for UCB Pharma

MPe: Grant/research support from UCB Pharma; Consultant for GSK, MedImmune, Merck Serono, Parexel and UCB Pharma

VS: Consultant for AbbVie, Afferent, Amgen, Biogen Idec, Bioventus, BMS, Carbylan, Celgene, Celltrion, CORRONA, Crescendo, Genentech.Roche, GSK, Hospira, Iroko, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi, SKK, Takeda, UCB Pharma, Vertex

MPi: Consultant for UCB Pharma

JM: Consultant for UCB Pharma

PL: None

CMN: Consultant for HGS, PGSK and UCB Pharma

SJ: None

FH: Consultant for UCB Pharma

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JO: None

SB: Employee of UCB Pharma

BK: Employee of UCB Pharma

CGa: Employee of UCB Pharma

KK: Bristol-Myers Squibb, Genentech, Biogen, IDEC Inc, Anthera, Cephalon, Cypress, MedImmune, Novo Nordisk, Zymogenetics, Serono, UCB Pharma

RF: Consultant for UCB Pharma

CGo: Consultant for GSK, MedImmune, Merck Serono and UCB Pharma

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TABLES AND FIGURES

TABLES

Table 1. Patient demographics and characteristics at the start of SL0008

	Safety population (n=203)
Age, years, mean (SD)	38.7 (11.0)
Female, n (%)	192 (94.6)
Ethnic group	
White, n (%)	158 (77.8)
Black, n (%)	20 (9.9)
Asian, n (%)	22 (10.8)
Other/mixed, n (%)	3 (1.5)
Immunosuppressives, n (%)	90 (44.3)
Antimalarials, n (%)	88 (43.3)
Corticosteroids (prednisone equivalent), n (%)	191 (94.1)
Dose, median mg/day (range)	10.0 (0-60)
None, n (%)	12 (5.9)
>0-5.0 mg/day, n (%)	53 (26.1)
>5.0-7.5 mg/day, n (%)	15 (7.4)
>7.5-12.5 mg/day, n (%)	64 (31.5)

>12.5-17.5 mg/day, n (%)	16 (7.9)
>17.5 mg/day, n (%)	43 (21.2)
Total BILAG score,* median (min, max)	14.0 (0, 57)
Total SLEDAI score, median (min, max)	10.0 (0, 34)
PGA (100 mm VAS),† median (min, max)	31.0 (0, 96)
PtGA (100 mm VAS),† median (min, max)	41.0 (0, 95)

*Total BILAG score was calculated according to the BILAG-2004 index convention: A=12, B=8, C=1, D=0, E=0. BILAG grades were determined for all 9 body systems by independent central readers. †Assessed on a scale of 0 (very good, asymptomatic, and no limitation of normal activities), to 100 (very poor, very severe symptoms which are intolerable, and inability to carry out all normal activities). The safety population consisted of all patients who received at least 1 dose (or partial dose) of study medication. BILAG: British Isles Lupus Assessment Group; PGA: Physician's Global Assessment of Disease Activity; PtGA: Patient's Global Assessment of Disease Activity; SD: Standard Deviation; SLE: Systemic Lupus Erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; VAS: Visual Analogue Scale.

Table 2. Summary of TEAEs during SL0008

	Safety population (n=203)		
	Patients, n	Patients, %	Number of events
Any TEAE	**192**	**94.6**	**1946**
Severe TEAEs	51	25.1	88
Discontinuations due to TEAEs	**29**	**14.3**	**35**
Drug-related TEAEs*	**87**	**42.9**	**300**
Serious TEAEs	**57**	**28.1**	**98**
Infusion reactions	**29**	**14.3**	**74**
Deaths†	**1**	**0.5**	**1**

The safety population consisted of all patients who received at least 1 dose (or partial dose) of epratuzumab. *TEAEs considered possibly, probably, or definitely related to the study drug by the investigator; †One death which was considered as unlikely to be related to the study drug by the investigator. TEAE: treatment-emergent adverse event.

Table 3. TEAEs occurring in ≥5% of patients by preferred term during SL0008

MedDRA v15.0 System Organ Class / Preferred Term	Safety population (n=203) Patients, n	Patients, %	No. of events	Incidence rate/100 patient-years
Any TEAE	192	94.6	1946	510.4
Blood and lymphatic system disorders	**40**	**19.7**	**65**	**17.0**
Iron deficiency anaemia	12	5.9	15	3.9
Cardiac disorders	**20**	**9.9**	**29**	**7.6**
Tachycardia	13	6.4	16	4.2
Ear and labyrinth disorders	**15**	**7.4**	**18**	**4.7**
Vertigo	12	5.9	14	3.7
Gastrointestinal disorders	**64**	**31.5**	**199**	**52.2**
Nausea	20	9.9	30	7.9
Vomiting	18	8.9	22	5.8

Diarrhoea	17	8.4	29	7.6
General disorders and administration site conditions	**63**	**31.0**	**150**	**39.3**
Asthenia	20	9.9	36	9.4
Pyrexia	14	6.9	29	7.6
Oedema peripheral	14	6.9	17	4.5
Fatigue	13	6.4	15	3.9
Infections and infestations	**138**	**68.0**	**487**	**127.7**
Upper respiratory tract infection	47	23.2	93	24.4
Urinary tract infection	50	24.6	87	22.8
Sinusitis	22	10.8	30	7.9
Nasopharyngitis	16	7.9	18	4.7
Bronchitis	18	8.9	23	6.0
Gastroenteritis	11	5.4	13	3.4
Viral infections	11	5.4	13	3.4
Musculoskeletal and connective tissue disorders	**77**	**37.9**	**170**	**44.6**
Systemic lupus	17	8.4	20	5.2

erythematosus				
Arthralgia	16	7.9	24	6.3
Back pain	14	6.9	25	6.6
Nervous system disorders	**79**	**38.9**	**154**	**40.4**
Headache	40	19.7	66	17.3
Dizziness	19	9.4	24	6.3
Psychiatric disorders	**36**	**17.7**	**59**	**15.5**
Depression	16	7.9	18	4.7
Anxiety	14	6.9	16	4.2
Respiratory, thoracic and mediastinal disorders	**53**	**26.1**	**101**	**26.5**
Dyspnoea	15	7.4	20	5.2
Cough	13	6.4	14	3.7
Oropharyngeal pain	11	5.4	13	3.4
Skin and subcutaneous tissue disorders	**54**	**26.6**	**100**	**26.2**
Rash	15	7.4	22	5.8
Vascular disorders	**38**	**18.7**	**52**	**13.6**

Hypertension	18	8.9	20	5.2

The safety population consisted of all patients who received at least 1 dose (or partial dose) of epratuzumab.

Table 4. Serious TEAEs occurring in ≥1.5% of patients by system organ class and preferred term during SL0008

MedDRA v15.0 System Organ Class / Preferred Term	Safety population (n=203) Patients, n	Patients, %	No. of events	Incidence rate/100 patient-years
Any serious TEAE	57	28.1	98	25.7
Blood and lymphatic system disorders	**5**	**2.5**	**5**	**1.3**
Gastrointestinal disorders	**3**	**1.5**	**16**	**4.2**
General disorders and administration site conditions	**3**	**1.5**	**3**	**0.8**
Hepatobiliary disorders	**3**	**1.5**	**3**	**0.8**
Cholelithiasis	3	1.5	3	0.8
Infections and infestations	**14**	**6.9**	**15**	**3.9**
Injury, poisoning and procedural complications	**3**	**1.5**	**3**	**0.8**
Musculoskeletal and connective	**11**	**5.4**	**14**	**3.7**

tissue disorders				
Systemic lupus erythematosus	7	3.4	7	1.8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3**	**1.5**	**6**	**1.6**
Nervous system disorders	**3**	**1.5**	**3**	**0.8**
Psychiatric disorders	**4**	**2.0**	**4**	**1.0**
Renal and urinary disorders	**7**	**3.4**	**7**	**1.8**
Lupus nephritis	4	2.0	4	1.0
Vascular disorders	**5**	**2.5**	**6**	**1.6**

The safety population consisted of all patients who received at least 1 dose (or partial dose) of epratuzumab.

FIGURE LEGENDS

Figure 1. EMBLEM™ and SL0008 study design and patient disposition

cd: cumulative dose; IV: intravenous; OLE: open-label extension; QW: every week; Q2W: every other week; RCT: randomized controlled trial; SOC: standard of care; TEAE: treatment-emergent adverse event.

Figure 2. Clinical efficacy of epratuzumab during SL0008: A) Median corticosteroid dose, B) Combined treatment response, C) Median total BILAG score,* D) Median total SLEDAI score

*Total BILAG score was calculated according to the BILAG-2004 index convention: A=12, B=8, C=1, D=0, E=0. BILAG grades were determined for all 9 body systems by independent central readers. Treatment response in this study was based on a modification of the BILAG-based Composite Lupus Assessment (BICLA) composite endpoint, defined as BILAG improvement without worsening, and no worsening in SLEDAI-2K or PGA; the fourth criteria of BICLA ("no treatment failure") was not included. Last visit: last available value for each patient during the EMLBEM™ OLE, regardless of

time of discontinuation. BILAG: British Isles Lupus Assessment Group; OLE: Open-label Extension; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

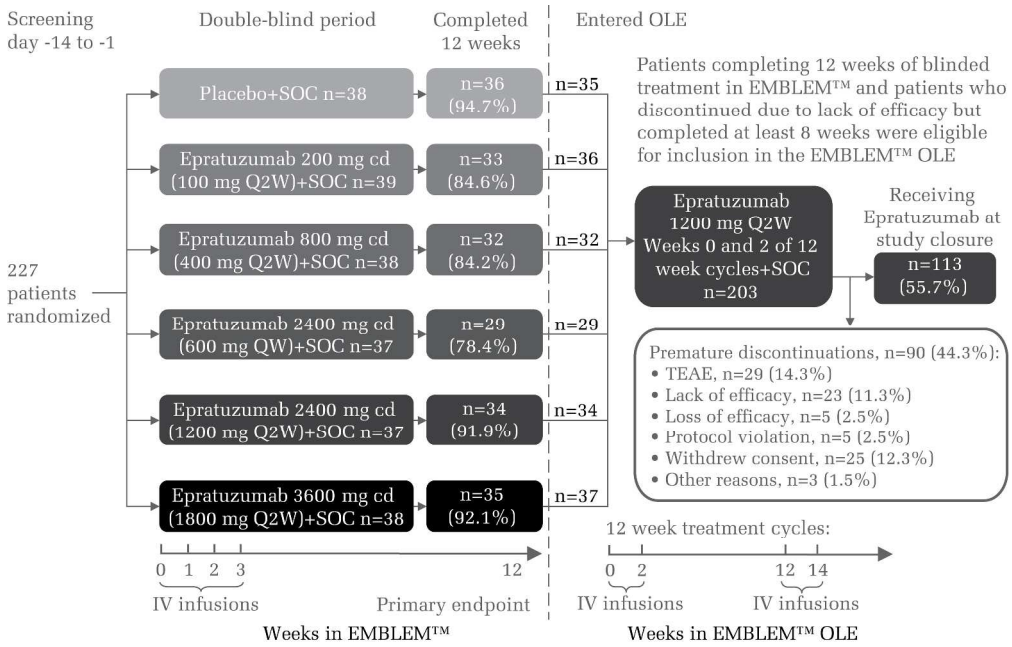

Figure 1. EMBLEM™ and SL0008 study design and patient disposition

cd: cumulative dose; IV: intravenous; OLE: open-label extension; QW: every week; Q2W: every other week; RCT: randomized controlled trial; SOC: standard of care; TEAE: treatment-emergent adverse event.
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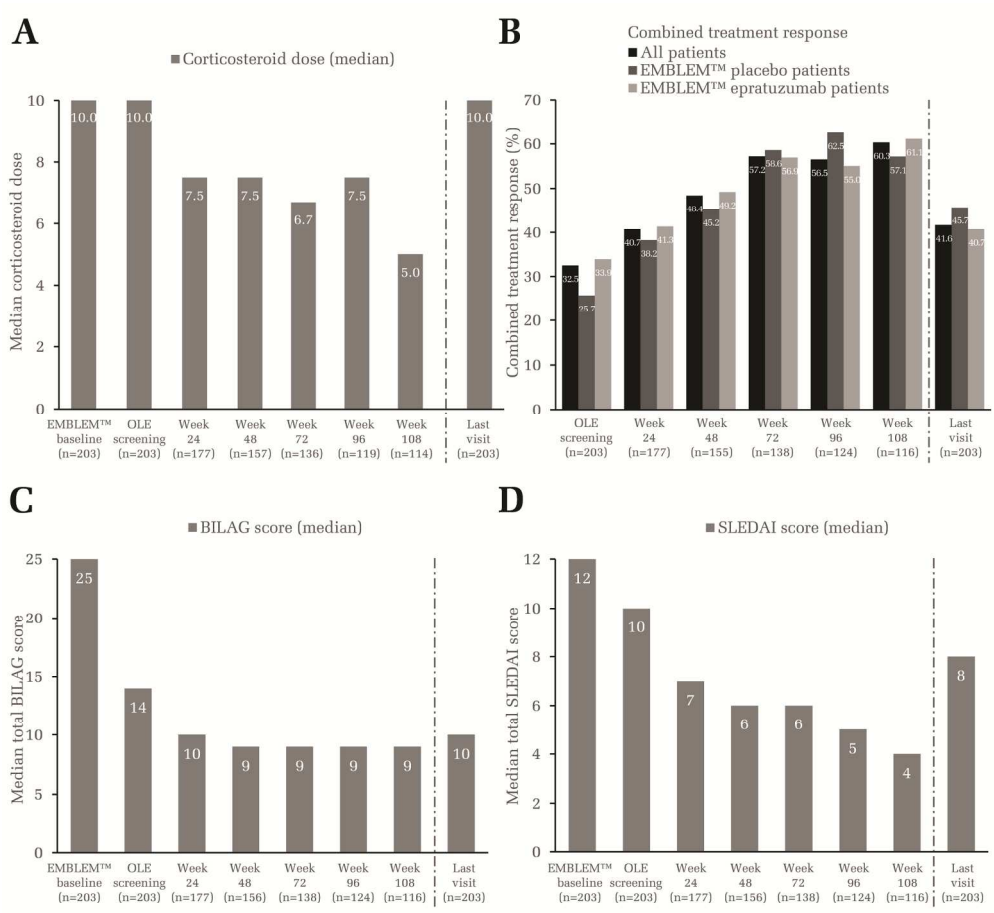

Clinical efficacy of epratuzumab during SL0008: A) Median corticosteroid dose, B) Combined treatment response, C) Median total BILAG score,* D) Median total SLEDAI score
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